REMARKS

Applicants have made two profound and seminal discoveries --- (1) amyloid pathology and pathogenic protein aggregation is present outside the central nervous system in the ocular lens, and (2) amyloidogenic disease-associated pathology in the lens manifests as protein aggregates (cataracts) within specific regions of an ocular lens, i.e., the supranuclear/deep cortical region compared to any other region of the lens. The claims are drawn to detecting aggregates in this very specific anatomical location (subregion of the lens) in which pathogenic protein aggregation does not commonly occur.

Cataracts occur in various types and subtypes which arise by different pathophysiologic mechanisms. Distinct types of cataracts have been associated with variousclinical or pathological conditions. (see Dorland's Medical Dictionary; Exhibit A). These different types of cataracts may reflect disease restricted to the lens or may represent lens-specific manifestations of systemic disease. For example, protein aggregation at the nucleus of the lens is termed a senile cataract, the most common cataract and is associated solely with the aging process. Cataracts associated with diabetes are bilateral, shaped like a snowflake and are located at the anterior and posterior cortical regions of the lens. A brightly colored, sunflower-shaped cataract with anterior capsular opacity occurs in patients with Wilson's disease and hypercupremia.

Applicants were the first to discover that a supranuclear cataract, i.e., protein aggregation and opacity in the deep cortex of the lens just above the nucleus (see Figs. 1A-G of the application) is a diagnostic marker for amyloid disorders and neurological conditions characterized by amyloid formation such as Alzheimer's Disease. This ground-breaking observation forms the basis for the invention - an antemortem method for diagnosing and monitoring an amyloid accumulation by detecting lens opacity (protein aggregation) within specific subregions of the lens, i.e., the supranucleus or deep cortex of the lens.

Claim 1 - 36 are pending. Claims 1, 5, 9, 19, and 20 were amended to require "deep" cortical; this amendment is supported by disclosure at page 4, line 24, of the specification. Claim 9 was amended to insert "or fragment thereof"; the amendment is supported by disclosure at page 3, line 15. New claims 34-36 were added. New claim 34 is supported by disclosure at page 9, lines 22-27, and at page 10, lines 26-29, of the specification. New claim 35 is supported

by disclosure at page1, lines 22-24. New claim 36 is supported by disclosure at page 28, lines 6-23, of the specification.

No new matter has been added by this amendment.

I. Objections to the Abstract

The Examiner has objected to Abstract, because it includes the implied phrase " The invention provides". The Abstract has been amended to delete the phrase.

II. Objections to the Claims

The Examiner objected to claim 2, because of the extraneous word "or". Applicants believe that the claim at issue is claim 3, rather than claim 2, and have amended claim 3 to delete the word "or".

III. Claim Rejections Under 35 U.S.C. § 103

Claims 1, 2, 4, 5, 7-9, 12, 14 15, 18-24, 28-30 and 31-33 were rejected for obviousness over Hageman in view on Nanjo et al. The Examiner states:

> Hageman discloses a method of identifying an amyloidogenic disorder in a mammal by studying Aβ amyloid protein accumulation in ocular tissue ([0264] [0274] [0288]. Hageman does not however teach detection of said aggregate in specific regions of the ocular lens. Nanjo et al. disclose a method of conducting ophthalmic measurements of protein accumulation in lens tissue by detecting said polypeptide aggregate in a supranuclear or cortical region of an ocular lens. Nanjo et al. teach analyzing protein accumulation in various layers of the lens such as cortex, capsule and nucleus (col. 6 lines 27-67, col. 7 lines 21-24).

Claim 1 is directed to diagnosing an amyloidogenic disorder by detecting a polypeptide aggregrate in a supranuclear or deep cortical region of an ocular lens. Hageman, on the other hand, describes examination of a completely different anatomical organ of the eye - the retina, more specifically the macula of the retina, and even more specifically drusen, an anatomically distinct deposit of eosinophilic material between the inner collagenous layer of Bruch's membrane and the retinal pigment epithelium (see [0036] of Hageman).

The lens and retina are anatomically, embryologically, and physiologically distinct organs within the eye (see diagram in Exhibit F), and the ocular lens of the eye is characterized by anatomically distinct sub regions (see diagrams in Exhibits B, C, D and E). The lens was not examined by Hageman, nor did Hageman make any suggestion to examine the very precise subregions of the lens, i.e., the supranuclear/deep cortical region of the lens, as required by the claims.

Moreover, Hageman makes no correlation whatsoever between detection of aggregrates and an amyloidogenic disorder. The passages to which the Examiner cites merely state that the eyes that were studied were part of a repository of human donor eyes from people with a variety of diseases - "Other ocular and systemic diseases including glaucoma, diabetes, other retinal and macular degenerations, Alzheimer's disease, Parkinson's disease, and a variety of developmental anomalies are also represented in the repository". This sentence in no way states or implies that an amyloidogenic disorder is in any way diagnosed by detecting polypeptide aggregates in the eye. Moreover, Hageman's Table A indicates that Amyloid β (Aβ), the hallmark of amyloidogenic disorders such as Alzheimer's Disease was not detected at all.

The secondary reference, Nanjo et al. describes an ophthalmic measurement device utilizing a laser beam and scattered light receiving system "to understand internal parts of an eyeball, especially protein particles of internal parts of crystalline lens by means of measurement has utility for detecting or diagnosing cataract in its early stage, or the like" (col. 1, lines 26-30 of Nanjo et al.). No particular anatomical region of the anterior region of the eye is highlighted as being particularly useful in the diagnosis of any particular disease, much less an amyloidogenic disorder (as recited in claim 1) or a neurodegenerative disorder (as recited in claim 31).

Independent claim 1 requires detecting aggregates in a very precise anatomical location of the eye - the supranuclear or deep cortical region of an ocular lens. Independent claim 14 requires detecting an increase the ratio of scattered light from the same region of the lens compared to the nuclear region. Figs. 1A-G show aggregation (cataracts) at various anatomically distinct locations of the ocular lens. For example, Fig. 1B shows aggregation in the supranuclear region (white dashed arc) as required by the claims as well as aggregation in the nuclear region (black arrow), a common and distinct age-related condition.

Although Nanjo et al. describe various parts of the lens - "lens capsule, a lens cortex, a viviparous lens nucleus, a senile lens nucleus and the like....." (col. 6, lines 43-45) , it is in the context of a describing how an examiner using the apparatus positions an aim-mark image by moving a joystick (paragraph spanning lines 27-47, of col. 6), not to suggest that a particular location within the eye is diagnostically significant for any particular disease. Thus, the combination of Hageman and Nanjo fail to describe or suggest a method of diagnosing an amyloid disorder or any other neurological disorder by detecting protein aggregrates in the specific subregions of the ocular lens required by the claims.

Claim 3, 16, and 17 depend from claim 1 and further require that the detecting step be carried out by a particular method of detection, e.g., Scheimflug optics, quasi-elastic light scattering, and Raman spectroscopy. These claims were rejected for obviousness over Hageman in view of Nanjo et al. in further view of Bursell et al. Although Bursell et al. describe the three detection methods, the description is in the context of detecting cholesterol generally in the lens. Bursell et al. neither describe nor suggest detection of protein aggregates in any particular region of the lens. Since none of the cited references, describe or suggest detection in a specific region of the lens, these claims are nonobvious over the cited art.

Claims 10, 12, and 13 were also rejected for obviousness; the examiner based this rejection on Hageman in view of Nanjo et al. in further view of Schenk. The rejected claims depend from claim 1 and require the protein aggregates to be a prion protein or an Aβ protein such as $A\beta_{1-42}$. This combination of references also fails to describe detection of aggregates in the specific regions of the lens required by the claims. Therefore, this rejection fails.

Claim 11, which depends from claim 1, further requires that the protein aggregate contain α-synclein. This claim was rejected for obviousness over Hageman in view of Nanjo as above in further view of Jensen et al. Jensen et al. describe a vaccination protocol for generating an immune response to one or more components of amyloid deposits including α-synclein. This reference provides no additional description of where to look for and detect protein aggregates, and thus, claim 11 is non-obvious over this combination of references.

Claims 26 and 27 were rejected for obviousness over Hageman in view of Nanjo in further view of Bursell. These claims depend from claim 19, which requires detecting scattered light from the supranuclear or deep cortical region of the lens, and further requires quasi-electric light scattering and Raman spectroscopy, respectively. As is discussed above, Hageman and

Nanjo do not describe or suggest examination of the supranuclear or deep cortical region of the lens. Bursell describes generally measuring light scattering from the lens but fails to describe the specific regions of the lens required by the claims - the fundamental basis of the claimed diagnostic procedure. The specific anatomical location of the heretofore unknown amyloidogenic disorder-associated cataract in the supranuclear and/or deep cortex of the lens is neither described nor suggested by any of the cited prior art. Applicant, therefore, requests that the Examiner withdraw this rejection.

CONCLUSION

Applicant submits that the application is in condition for allowance and such action is respectfully requested. Should any questions or issues arise concerning the application, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

Respectfully submitted,

Ingrid A. Beattie, Reg. No. 42,306
Attorney for Applicant
MINTZ, LEVIN, COHN, FERRIS
GLOVSKY and POPEO, P.C.
One Financial Center
Boston, Massachusetts 02111
Tel: (617) 542-6000
Customer No. **30623**

TRA 2048776v1